The science, medicine, and future of contraception

The prevalence of contraceptive use is increasing worldwide, and in many countries more than 75% of couples use effective methods.[1] Existing methods of contraception are not perfect, however, and their acceptability is limited by side effects and inconvenience. Even in developed countries where contraception is freely available, many unplanned pregnancies occur. Thus, there is a real need for new methods of contraception that are more effective, easier to use, and safer than existing methods. In this article, we discuss current research into new forms of contraception and predict what methods are likely to be used in the future.

SOCIAL INFLUENCES

Demographic forces, prevalence of disease, and social and cultural factors influence not only the use of contraceptives but also the development of new methods. The age of onset of sexual activity is falling, whereas childbearing is being delayed or, in many developed countries, forgone altogether. The public presses for more "natural products," which are perceived to be safer, but at the same time demands that contraceptives have almost perfect efficacy.

Those concerned with the development of new drugs and devices assume the need for efficacy and are now seeking positive health benefits—methods that prevent not only pregnancy but also sexually transmitted disease and, in the long term, common diseases such as breast cancer. Heterosexual intercourse is now the main route of transmission of the human immunodeficiency virus. Although barrier methods such as condoms reduce the risk of transmission, there is a pressing need for additional and complementary methods of protection in the form of topical virucidal agents that ideally would also be spermicidal.

HORMONAL CONTRACEPTION FOR WOMEN

Methods involving steroid hormones have dominated new developments in contraception, and in the past 40 years more than 200 million women worldwide have taken "the pill."[2] Recent data confirm its excellent safety, and in many respects the pill will be hard to beat. In the past 15 years, new developments in contraception have come mainly from tinkering with hormonal methods—new delivery systems (implants and hormone-releasing intrauterine devices), better progestogens, and lower doses of estrogen.

NEW DELIVERY SYSTEMS AND SELECTIVE RECEPTOR MODULATORS

In the early part of the 21st century, we will probably see the licensing of contraceptive vaginal rings, transdermal patches, and gels. In the longer term, selective modulators of hormone receptors will likely replace currently available estrogens and progestins to avoid their risks, particularly venous thrombosis, while reducing the incidence of common diseases such as breast cancer. Study of the molecular structure of hormone receptors has revealed that each ligand induces an almost unique conformational change and, hence, has slightly different biologic effects.[3] Therefore, organ-specific drugs, which produce the desired effect only on critical reproductive processes, will likely become available.

ANTIPROGESTINS

The most exciting development in the past 20 years has been the discovery of compounds that antagonize the action of progesterone. Progesterone is necessary for the establishment and maintenance of pregnancy. Key events—including ovulation, fertilization, and implantation—depend on the secretion of progesterone by the ovary at the appropriate time. It is nearly 20 years since the discovery of the first antagonist of progesterone (mifepristone), which was shown to interrupt pregnancy. The political controversy surrounding the "abortion pill" has im-

Predicted developments

Within 5 years

- New delivery systems of conventional contraceptives, such as vaginal rings, transdermal patches, and gels
- Contraceptives that also protect against sexually transmitted disease

Short term (<10 years)

- "Once a month" pill that inhibits implantation
- Antiprogestins used for estrogen-free, daily pill for women
- Orally active, non-peptide antagonists of gonadotrophin-releasing hormone for men and women

Long term (>10 years)

- Antagonists of follicle stimulating hormone receptor
- Arrest of spermatogenesis or sperm maturation
- Arrest of final maturation of oocyte, such as with phosphodiesterase inhibitors
- Inhibitors of follicle rupture

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peded research into other possible uses of these compounds, including contraception.

Some years ago, Glasier et al showed that a single dose of 600 mg of mifepristone was highly effective as an emergency contraceptive after unprotected intercourse.[4] The compound both inhibits ovulation and prevents implantation, properties which suggest that it could be used as a regular form of contraception. A daily dose of 2 to 5 mg (less than a hundredth of the dose required to induce abortion) inhibits ovulation and prevents the formation of a secretory endometrium.[5] Estrogen secretion by the ovary is maintained at the level of that found in the follicular phase of the menstrual cycle. Preliminary data suggest that most women are amenorrheic while taking the antiprogestin, which could be a considerable advantage over other forms of estrogen-free contraceptives, such as gestagen-only pills.

Antigestagens might also be used for "once-a-month" pills. If they are given in the early luteal phase of the cycle, the formation of a secretory endometrium is retarded without affecting the regular pattern of menstruation. In a pilot study of 21 women in Sweden who used this method as their sole means of contraception, only 1 pregnancy occurred in 153 menstrual cycles.[6] A major practical problem with this approach is the difficulty in detecting ovulation so that the pill can be taken at the correct time of the cycle. A once-a-month pill that prevented ovulation or implantation would be welcomed by many women from various countries and cultures.[7] In contrast, only a few women would be prepared to use a pill taken around the time of expected menses, when implantation of the embryo would already have occurred. In any case, current evidence suggests that mifepristone alone or in combination with misoprostol would result in too high an incidence of pregnancy to be useful as a regular method of inducing early menses.[8]

CONTRAGESTION

It has also been proposed that mifepristone could be taken only if the menses was overdue ("contragestion"). An inducer of a missed menses acts by disrupting an implanted embryo and induces an early abortion. A pilot study supported by the World Health Organization reported few ongoing pregnancies in women given a combination of mifepristone, 600 mg, and the prostaglandin analogue gemeprost, 1 mg, within 10 days of their expected menses.[9] Although this study showed "proof of concept," legal, political, and ethical issues make it unlikely that this approach would receive widespread acceptance. Moreover, in that study there was considerable variation in the timing of the onset of the next menses, which would make it difficult for women to decide whether to take the pill again in subsequent cycles. For those women who find it ethically acceptable, a pill that induced missed menses might be more attractive than a monthly pill to induce early menses, perhaps because it would be required only 2 or 3 times a year.

HORMONAL CONTRACEPTION FOR MEN

Evidence from different countries and cultures shows a growing demand for more effective and convenient methods of contraception for men.[10] A recent survey in Scotland, South Africa, Hong Kong, and China found that most men would consider using a "male pill." Although it has been known for nearly 50 years that azoospermia can be induced by the administration of large doses of testosterone, progress in the development of hormonal male contraception has been slow for several reasons. The supraphysiologic dose of androgen required to induce azoospermia causes adverse effects, including prostatic hypertrophy and unfavorable changes in plasma lipid levels, precluding wide-scale use in otherwise healthy men.[11]

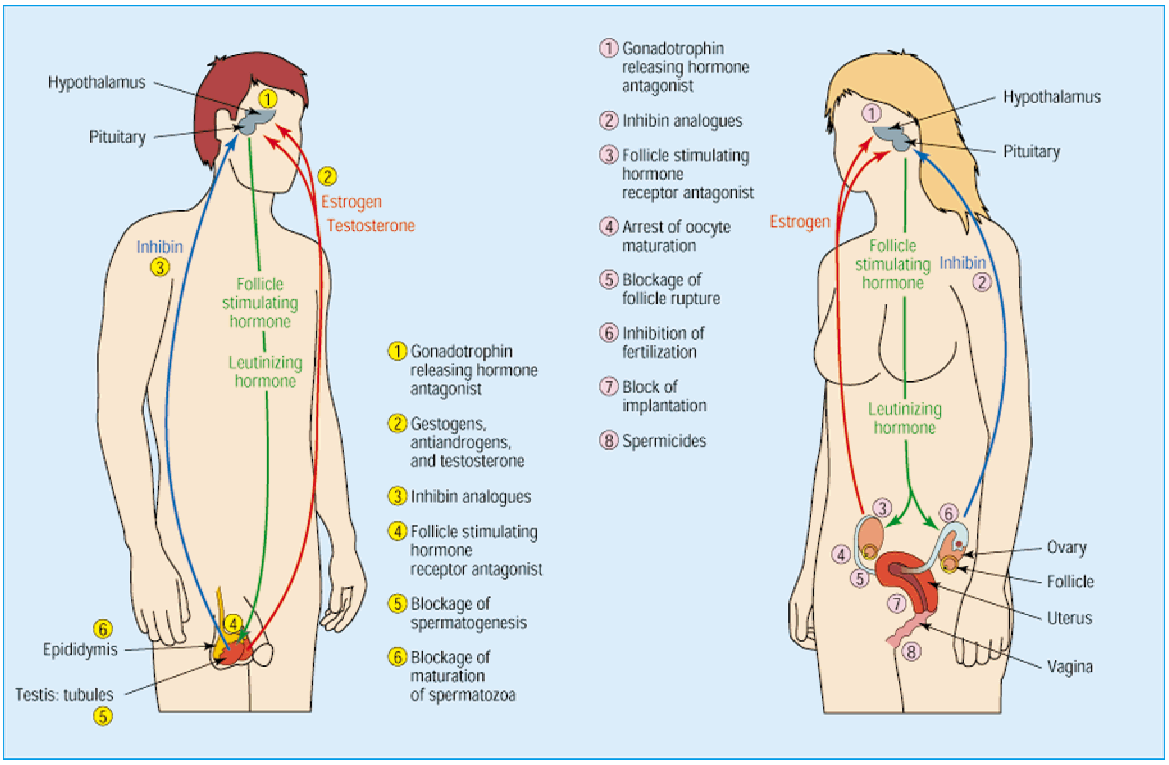
Current research, therefore, focuses on lower physiologic doses of androgen in combination with gestagens (such as desogestrel and cyproterone acetate) or gonadotropin-releasing hormone antagonists.[12] Orally active nonpeptide antagonists of gonadotropin-releasing hormone or a depot preparation could provide a practical method of suppressing gonadotropins in combination with androgen replacement. However, no convenient, safe preparations of androgen currently exist for replacement therapy, although this is the subject of research by several pharmaceutical companies. Encouraging progress is being made in the development of new androgens (such as 7α-methyl nortestosterone) that have possible health benefits and in new methods of long-term delivery of steroids in implants (such as Implanon).[13] The development of a safe, acceptable treatment that is as effective as the combined oral contraceptive pill for women (Pearl index [measure of effectiveness] 1/100 woman-years) is at least 5 years away.

BEYOND 2010

In the long term, there are several possible approaches for contraception in men and women (figure).[14]

Meiotic arrest

In both sexes, the formation of gametes (spermatogenesis and oogenesis) involves the process of meiosis, whereby the number of chromosomes in a diploid nucleus is halved to the haploid state by cell division. Meiosis occurs only in germ cells, and hence, substances that interfere with meiotic division should be specific for the gonad. Specific genes are expressed at different stages of spermatogenesis,



Potential targets for contraception in men and women

and antagonism of their products (such as activin) could lead to sterility.

In the female, meiosis is almost completed during fetal development, but the final stages of meiotic division are delayed into adulthood, until just before ovulation. If we knew the mechanism by which meiosis was arrested in the oocyte, it might be possible to activate a similar mechanism to inhibit spermatogenesis in men. The arrest of meiosis in the oocyte involves at least 1 protein specific to germ cells (c-Mos), which is also transcribed in the male during meiosis. A high concentration of adenosine 3′,5′-cyclic monophosphate (cyclic AMP) is apparently important in preventing final maturation of the oocyte, and specific inhibition of phosphodiesterase 3 (the enzyme that catalyzes the breakdown of cyclic AMP) is contraceptive in rats, preventing the oocyte from acquiring developmental competence.

Blockage of follicle-stimulating hormone

Blocking the follicle-stimulating hormone receptor or inhibiting the secretion of follicle-stimulating hormone with analogues of inhibin will interfere with spermatogenesis, although whether sperm production can be maintained by testosterone alone in men, as it can in rodents, is not known. A minimum concentration of testosterone within the testis is probably required for spermatogenesis, so that inhibitors of androgen synthesis or action will be contraceptive. The key to the successful use of these approaches is again specificity. It may be possible to use the follicle-stimulating hormone receptor as a target to deliver another agent specifically to the testis.

Mutations of the follicle-stimulating hormone receptor have been described in women who present with primary amenorrhea due to a lack of follicle development. Inhibitors of follicle-stimulating hormone synthesis or action could prevent fertility but would require estrogen replacement to prevent the consequences of hypoestrogenism. Arresting final maturation of the oocyte before ovulation or follicle rupture would be a desirable method of contraception that did not disrupt the endocrine events controlling the ovarian cycle.

Preventing implantation

Progesterone induces the transcription of various endometrial gene products involved in implantation—for example, leukemic inhibitory factor, calcitonin, vitronectin, $\alpha_v\beta_3$ integrin, and $\alpha_4\beta_1$ integrin.[15,16] Specific antagonists of these products would be promising as new contraceptives because they should act only at the uterus.

The formation of new blood vessels (angiogenesis) is usually restricted in adults to the repair of injury, but in the ovary and uterus extensive angiogenesis occurs each

month during the formation of the follicle, corpus luteum, and endometrium. A potent antagonist of vascular endothelial growth factor prevented pregnancy in mice without producing major adverse systemic effects in the long term.[17]

Immunization

Other likely targets for new contraceptives are proteins involved in fertilization.[18,19] The sperm attaches to the egg through the interaction of specific antigens on the sperm surface with the zona pellucida proteins of the egg (such as ZP3). Immunizing female monkeys with zona pellucida proteins prevents pregnancy, but unfortunately produces a form of autoimmune oophoritis with loss of oocytes and premature menopause. Unforeseen consequences resulting from autoimmunity are a potential hazard of antifertility vaccines. Immunization of women against sperm antigens should avoid such problems, but research is still at the initial stages.[20]

Another possibility is disrupting the synthesis or delivery of proteins such as fertilin that are important for the function of sperm membrane, thus leading to incompetent spermatozoa. Interfering with the final maturation of spermatozoa has the attraction that it would result in sperm that were incompetent to fertilize an egg without running the risk of producing genetically mutated germ cells. However, concerns have been raised about the possible misuse of contraceptive vaccines, particularly if they are not fully reversible.

Because of these political concerns and doubt about the long-term consequences of immunization, there is little commercial enthusiasm for further development of this approach despite the scientific potential.

CONCLUSIONS

Compared with many drugs, the development of a new contraceptive product is expensive and relatively high risk. The pattern of contraceptive use is unlikely to change radically in the next 10 years. No one method will be suitable for everyone, and personal preferences will probably change through each reproductive life. In the next 5 years, more sophisticated systems for the delivery of steroid hormones, through or under the skin and into the uterus, will extend the range of options available. In 5 to 10 years, new steroid antagonists such as antiprogestins will replace some current contraceptive methods, such as gestagen-only pills, and probably lead to new approaches like a once-a-month pill. By 10 to 15 years, the dream of an effective, safe male pill will probably become a reality, shifting the burden of responsibility for contraception more equally between men and women. Only then will women have truly achieved "the fifth freedom"—freedom from the burden of excessive fertility.[21]

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